# Retina Organoid Transplants Develop Photoreceptors and Improve Visual Function in RCS Rats With RPE Dysfunction.

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**Funding Grants:** Restoring vision by sheet transplants of retinal progenitors and retinal pigment epithelium (RPE) derived from human embryonic stem cells (hESCs), Morphological and functional integration of stem cell derived retina organoid sheets into degenerating retina models

**Public Summary:**
The light-sensitive cells of the eye (photoreceptors) depend on the support of retinal pigment epithelium (RPE). This study investigate whether human embryonic stem cell (hESC) derived retinal organoids (mainly photoreceptor progenitors) improve vision in a rat model with defective RPE, the Royal College of Surgeons (RCS) rat. In this report, we demonstrate that CSC14 hESC-derived retinal organoid sheets can be transplanted to RCS rats, develop mature photoreceptors and other retinal cells, ultimately improving visual function. This study suggests transplantation of retinal organoid sheets may be a promising future therapy for retinal diseases.

**Scientific Abstract:**
Purpose: To study if human embryonic stem cell-derived photoreceptors could survive and function without the support of retinal pigment epithelium (RPE) after transplantation into Royal College of Surgeons rats, a rat model of retinal degeneration caused by RPE dysfunction. Methods: CSC14 human embryonic stem cells were differentiated into primordial eye structures called retinal organoids. Retinal organoids were analyzed by quantitative PCR and immunofluorescence and compared with human fetal retina. Retinal organoid sheets (30-70 day of differentiation) were transplanted into immunodeficient RCS rats, aged 44 to 56 days. The development of transplant organoids in vivo in relation to the host was examined by optical coherence tomography. Visual function was assessed by optokinetic testing, electroretinogram, and superior colliculus electrophysiologic recording. Cryostat sections were analyzed for various retinal, synaptic, and donor markers. Results: Retinal organoids showed similar gene expression to human fetal retina transplanted rats demonstrated significant improvement in visual function compared with RCS nonsurgery and sham surgery controls by ERGs at 2 months after surgery (but not later), optokinetic testing (up to 6 months after surgery) and electrophysiologic superior colliculus recordings (6-8 months after surgery). The transplanted organoids survived more than 7 months; developed photoreceptors with inner and outer segments, and other retinal cells; and were well-integrated within the host. Conclusions: This study, to our knowledge, is the first to show that transplanted photoreceptors survive and function even with host's dysfunctional RPE. Our findings suggest that transplantation of organoid sheets from stem cells may be a promising approach/therapeutic for blinding diseases.